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Dated 19 January 2004

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1. Your reference — **P032756GB**

19 DEC 2002
20DEC02 E772366-1 D00019
P01/7700 0.00-0229618.4

2. Patent application number *(The Patent Office will fill in this pa* — 0229618.4

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

CANCER RESEARCH TECHNOLOGY LTD
61 Lincoln's Inn Fields
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WC2A 3PX
(For further applicants please see continuation sheet)

Patents ADP number *(if you know it)* — 8497927002

If the applicant is a corporate body, give the country/state of its incorporation — **UNITED KINGDOM**

4. Title of the invention

PYRAZOLE COMPOUNDS

5. Name of your agent *(if you have one)*

Carpmaels & Ransford

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

43 Bloomsbury Square
London
WC1A 2RA

Patents ADP number *(if you know it)* — **83001**

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body

See note (d))

Yes

Additional Applicant:-

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State of Incorporation:

UNITED KINGDOM 8173940002

Additional Applicant:-

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State of Incorporation:

UNITED KINGDOM 8522195001

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Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature: Carpmaels & Ransford

Date: 19th December 2002

12. Name and daytime telephone number of person to contact in the United Kingdom: **P.N. HOWARD** **020-7242 8692**

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Pyrazole Compounds

This invention relates to substituted pyrazoles having HSP90 inhibitory activity, to the use of such compounds in medicine, in relation to diseases which are mediated by excessive or inappropriate HSP90 activity such as cancers, and to pharmaceutical compositions containing such compounds.

Background to the invention

Molecular chaperones maintain the appropriate folding and conformation of proteins and are crucial in regulating the balance between protein synthesis and degradation. They have been shown to be important in regulating many important cellular functions, such as cell proliferation and apoptosis (Jolly and Morimoto, 2000; Smith et al., 1998; Smith, 2001).

Heat Shock Proteins (HSPs)

Exposure of cells to a number of environmental stresses, including heat shock, alcohols, heavy metals and oxidative stress, results in the cellular accumulation of a number of chaperones, commonly known as heat shock proteins (HSPs). Induction of HSPs protects the cell against the initial stress insult, enhances recovery and leads to maintenance of a stress tolerant state. It has also become clear, however, that certain HSPs may also play a major molecular chaperone role under normal, stress-free conditions by regulating the correct folding, degradation, localization and function of a growing list of important cellular proteins.

A number of multigene familes of HSPs exist, with individual gene products varying in cellular expression, function and localization. They are classified according to molecular weight, e.g., HSP70, HSP90, and HSP27
Several diseases in humans can be acquired as a result of protein misfolding (reviewed in Tytell et al., 2001; Smith et al., 1998). Hence the development of therapies which disrupt the molecular chaperone machinery may prove to be beneficial. In some conditions (e.g., Alzheimer's disease, prion diseases and Huntington's disease), misfolded proteins can cause protein aggregation resulting in neurodegenerative disorders. Also, misfolded proteins may result

in loss of wild type protein function, leading to deregulated molecular and physiological functions in the cell.

HSPs have also been implicated in cancer. For example, there is evidence of differential expression of HSPs which may relate to the stage of tumour progression (Martin et al., 2000; Conroy et al., 1996; Kawanishi et al., 1999; Jameel et al., 1992; Hoang et al., 2000; Lebeau et al., 1991). As a result of the involvement of HSP90 in various critical oncogenic pathways and the discovery that certain natural products with anticancer activity are targeting this molecular chaperone, the fascinating new concept has been developed that inhibiting HSP function may be useful in the treatment of cancer. The first molecular chaperone inhibitor is currently undergoing clinical trials.

HSP90

HSP90 constitutes about 1-2% of total cellular protein, and is usually present in the cell as a dimer in association with one of a number of other proteins (see, e.g., Pratt, 1997). It is essential for cell viability and it exhibits dual chaperone functions (Young et al., 2001). It plays a key role in the cellular stress response by interacting with many proteins after their native conformation has been altered by various environmental stresses, such as heat shock, ensuring adequate protein folding and preventing non-specific aggregation (Smith et al., 1998). In addition, recent results suggest that HSP90 may also play a role in buffering against the effects of mutation, presumably by correcting the inappropriate folding of mutant proteins (Rutherford and Lindquist, 1998). However, HSP90 also has an important regulatory role. Under normal physiological conditions, together with its endoplasmic reticulum homologue GRP94, HSP90 plays a housekeeping role in the cell, maintaining the conformational stability and maturation of several key client proteins. These can be subdivided into three groups: (a) steroid hormone receptors, (b) Ser/Thr or tyrosine kinases (e.g., ERBB2, RAF-1, CDK4, and LCK), and (c) a collection of apparently unrelated proteins, e.g., mutant p53 and the catalytic subunit of telomerase hTERT. All of these proteins play key regulatory roles in many physiological and biochemical

processes in the cell. New HSP90 client proteins are continuously being identified.

The highly conserved HSP90 family in humans consists of four genes, namely the cytosolic HSP90α and HSP90β isoforms (Hickey et al., 1989), GRP94 in the endoplasmic reticulum (Argon et al., 1999) and HSP75/TRAP1 in the mitochondrial matrix (Felts et al., 2000). It is thought that all the family members have a similar mode of action, but bind to different client proteins depending on their localization within the cell. For example, ERBB2 is known to be a specific client protein of GRP94 (Argon et al., 1999) and type 1 tumour necrosis factor receptor (TNFR1) and RB have both been shown to be clients of TRAP1 (Song et al., 1995; Chen et al., 1996).

HSP90 participates in a series of complex interactions with a range of client and regulatory proteins (Smith, 2001). Although the precise molecular details remain to be elucidated, biochemical and X-ray crystallographic studies (Prodromou et al., 1997; Stebbins et al., 1997) carried out over the last few years have provided increasingly detailed insights into the chaperone function of HSP90.

Following earlier controversy on this issue, it is now clear that HSP90 is an ATP-dependent molecular chaperone (Prodromou et al, 1997), with dimerization of the nucleotide binding domains being essential for ATP hydrolysis, which is in turn essential for chaperone function (Prodromou et al, 2000a). Binding of ATP results in the formation of a toroidal dimer structure in which the N terminal domains are brought into closer contact with each other resulting in a conformational switch known as the 'clamp mechanism' (Prodromou and Pearl, 2000b).

Known HSP90 Inhibitors

The first class of HSP90 inhibitors to be discovered was the benzoquinone ansamycin class, which includes the compounds herbimycin A and

geldanamycin. They were shown to reverse the malignant phenotype of fibroblasts transformed by the v-*Src* oncogene (Uehara et al., 1985), and subsequently to exhibit potent antitumour activity in both *in vitro* (Schulte et al., 1998) and *in vivo* animal models (Supko et al., 1995).

Immunoprecipitation and affinity matrix studies have shown that the major mechanism of action of geldanamycin involves binding to HSP90 (Whitesell et al., 1994; Schulte and Neckers, 1998). Moreover, X-ray crystallographic studies have shown that geldanamycin competes at the ATP binding site and inhibits the intrinsic ATPase activity of HSP90 (Prodromou et al., 1997; Panaretou et al., 1998). This in turn prevents the formation of mature multimeric HSP90 complexes capable of chaperoning client proteins. As a result, the client proteins are targeted for degradation via the ubiquitin proteasome pathway. 17-Allylamino, 17-demethoxygeldanamycin (17AAG) retains the property of HSP90 inhibition resulting in client protein depletion and antitumour activity in cell culture and xenograft models (Schulte et al, 1998; Kelland et al, 1999), but has significantly less hepatotoxicity than geldanamycin (Page et al, 1997). 17AAG is currently being evaluated in Phase I clinical trials.

Radicicol is a macrocyclic antibiotic shown to reverse the malignant phenotype of v-*Src* and v-*Ha-Ras* transformed fibroblasts (Kwon et al, 1992; Zhao et al, 1995). It was shown to degrade a number of signalling proteins as a consequence of HSP90 inhibition (Schulte et al., 1998). X-ray crystallographic data confirmed that radicicol also binds to the N terminal domain of HSP90 and inhibits the intrinsic ATPase activity (Roe et al., 1998). Radicicol lacks antitumour activity *in vivo* due to the unstable chemical nature of the compound.

Coumarin antibiotics are known to bind to bacterial DNA gyrase at an ATP binding site homologous to that of the HSP90. The coumarin, novobiocin, was shown to bind to the carboxy terminus of HSP90, i.e., at a different site to that occupied by the benzoquinone ansamycins and radicicol which bind at the N-terminus (Marcu et al., 2000b). However, this still resulted in inhibition

of HSP90 function and degradation of a number of HSP90-chaperoned signalling proteins (Marcu et al., 2000a). Geldanamcyin cannot bind HSP90 subsequent to novobiocin; this suggests that some interaction between the N and C terminal domains must exist and is consistent with the view that both sites are important for HSP90 chaperone properties.

A purine-based HSP90 inhibitor, PU3, has been shown to result in the degradation of signalling molecules, including ERBB2, and to cause cell cycle arrest and differentiation in breast cancer cells (Chiosis et al., 2001).

HSP90 as a Therapeutic Target

Due to its involvement in regulating a number of signalling pathways that are crucially important in driving the phenotype of a tumour, and the discovery that certain bioactive natural products exert their effects via HSP90 activity, the molecular chaperone HSP90 is currently being assessed as a new target for anticancer drug development (Neckers et al., 1999).

The predominant mechanism of action of geldanamycin, 17AAG, and radicicol involves binding to HSP90 at the ATP binding site located in the N-terminal domain of the protein, leading to inhibition of the intrinsic ATPase activity of HSP90 (see, e.g., Prodromou et al., 1997; Stebbins et al., 1997; Panaretou et al., 1998).

Inhibition of HSP90 ATPase activity prevents recruitment of co-chaperones and encourages the formation of a type of HSP90 heterocomplex from which these client proteins are targeted for degradation via the ubiquitin proteasome pathway (see, e.g., Neckers et al., 1999; Kelland et al., 1999).

Treatment with HSP90 inhibitors leads to selective degradation of important proteins involved in cell proliferation, cell cycle regulation and apoptosis, processes which are fundamentally important in cancer.

Inhibition of HSP90 function has been shown to cause selective degradation of important signalling proteins involved in cell proliferation, cell cycle

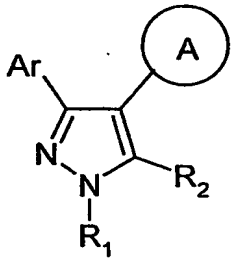
regulation and apoptosis, processes which are fundamentally important and which are commonly deregulated in cancer (see, e.g., Hostein et al., 2001). An attractive rationale for developing drugs against this target for use in the clinic is that by simultaneously depleting proteins associated with the transformed phenotype, one may obtain a strong antitumour effect and achieve a therapeutic advantage against cancer versus normal cells. These events downstream of HSP90 inhibition are believed to be responsible for the antitumour activity of HSP90 inhibitors in cell culture and animal models (see, e.g., Schulte et al., 1998; Kelland et al., 1999).

Brief description of the invention

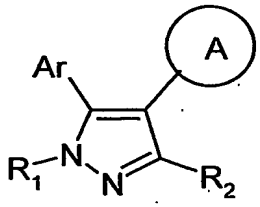
The present invention makes available a new class of substituted pyrazole compounds, which are HSP90 inhibitors and which inhibit cancer cell proliferation. Aromatic substitution on one ring carbon atom and non-aromatic carbocyclic or heterocyclic substitution on an adjacent ring carbon atom are principle characterising features of the compounds of the invention.

Detailed description of the invention

According to the present invention there is provided a compound of formula (IA) or (IB) or a salt, N-oxide, hydrate or solvate thereof:



(IA)



(IB)

wherein

Ar is an optionally substituted aryl or heteroaryl radical;

R_1 is hydrogen or optionally substituted C_1-C_6 alkyl;

R_2 is hydrogen, optionally substituted cycloalkyl, cycloalkenyl, C_1-C_6 alkyl, C_1-C_6 alkenyl, or C_1-C_6 alkynyl; or a carboxyl, carboxamide or carboxyl ester group; and;

ring A is a non aromatic carbocyclic or heterocyclic ring wherein (i) a ring carbon is optionally substituted, and/or (ii) a ring nitrogen is optionally substituted by a group of formula $-(Alk^1)_p-(Z)_r-(Alk^2)_s-Q$ where

Alk^1 and Alk^2 are optionally substituted C_1-C_3 alkyl,

p, r and s are independently 0 or 1,

Z is –O-, -S-, -(C=O)-, $-SO_2-$, -C(=O)O-, $-C(=O)NR^A-$, $-SO_2NR^A-$, $-NR^AC(=O)-$, $-NR^ASO_2-$ or $-NR^A-$ wherein R^A is hydrogen or C_1-C_6 alkyl, and

Q is hydrogen or an optionally substituted carbocyclic or heterocyclic radical.

When R_1 in compounds IA and IB is hydrogen, then compounds IA and IB are tautomeric forms of the same compound.

As used herein:

the term "carboxyl group" refers to a group of formula -COOH;

the term "carboxyl ester group" refers to a group of formula -COOR, wherein R is a radical actually or notionally derived from the hydroxyl compound ROH; and

the term " carboxamide group" refers to a group of formula $-CONR_aR_b$, wherein $-NR_aR_b$ is a primary or secondary (including cyclic) amino group actually or notionally derived from ammonia or the amine HNR_aR_b.

As used herein, the term "(C_1-C_6)alkyl" refers to a straight or branched chain alkyl radical having from 1 to 6 carbon atoms, including for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl and n-hexyl.

As used herein, the term "(C_1-C_6)alkenyl" refers to a straight or branched chain alkenyl radical having from 2 to 6 carbon atoms and containing at least one double bond of E or Z configuration, including for example, ethenyl and allyl.

As used herein, the term "(C_1-C_6)alkynyl" refers to a straight or branched chain alkenyl radical having from 2 to 6 carbon atoms and containing at least one triple bond, including for example, ethynyl and prop-2-ynyl.

As used herein the term "cycloalkyl" refers to a saturated carbocyclic radical having from 3-8 carbon atoms and includes, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

As used herein the term "cycloalkenyl" refers to a carbocyclic radical having from 3-8 carbon atoms containing at least one double bond, and includes, for example, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

As used herein the term "aryl" refers to a mono-, bi- or tri-cyclic carbocyclic aromatic radical. Illustrative of such radicals are phenyl, biphenyl and napthyl.

As used herein the term "carbocyclic" refers to a cyclic radical whose ring atoms are all carbon, and includes monocyclic aryl, cycloalkyl and cycloalkenyl radicals.

As used herein the term "heteroaryl" refers to a mono-, bi- or tri-cyclic aromatic radical containing one or more heteroatoms selected from S, N and O. Illustrative of such radicals are thienyl, benzthienyl, furyl, benzfuryl, pyrrolyl, imidazolyl, benzimidazolyl, thiazolyl, benzthiazolyl, isothiazolyl, benzisothiazolyl, pyrazolyl, oxazolyl, benzoxazolyl, isoxazolyl, benzisoxazolyl, isothiazolyl, triazolyl, benztriazolyl, thiadiazolyl, oxadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, indolyl and indazolyl.

As used herein the unqualified term "heterocyclyl" or "heterocyclic" includes "heteroaryl" as defined above, and in particular means a mono-, bi- or tri-cyclic non-aromatic radical containing one or more heteroatoms selected from S, N and O, and to groups consisting of a monocyclic non-aromatic radical containing one or more such heteroatoms which is covalently linked to another such radical or to a monocyclic carbocyclic radical. Illustrative of such radicals are pyrrolyl, furanyl, thienyl, piperidinyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thiadiazolyl, pyrazolyl, pyridinyl, pyrrolidinyl, pyrimidinyl, morpholinyl, piperazinyl, indolyl, morpholinyl, benzfuranyl, pyranyl, isoxazolyl, benzimidazolyl, methylenedioxyphenyl, ethylenedioxyphenyl, maleimido and succinimido groups.

Unless otherwise specified in the context in which it occurs, the term "substituted" as applied to any moiety herein means substituted with up to four substituents, each of which independently may be $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, hydroxy, hydroxy$(C_1\text{-}C_6)$alkyl, mercapto, mercapto$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkylthio, halo (including fluoro and chloro), trifluoromethyl, trifluoromethoxy, nitro, nitrile (-CN), oxo, phenyl, -COOH, $-COOR^A$, $-COR^A$, $-SO_2R^A$, $-CONH_2$, $-SO_2NH_2$, $-CONHR^A$, $-SO_2NHR^A$, $-CONR^AR^B$, $-SO_2NR^AR^B$, $-NH_2$, $-NHR^A$, $-NR^AR^B$, $-OCONH_2$, $-OCONHR^A$, $-OCONR^AR^B$, $-NHCOR^A$, $-NHCOOR^A$, $-NR^BCOOR^A$, $-NHSO_2OR^A$, $-NR^BSO_2OR^A$, $-NHCONH_2$, $-NR^ACONH_2$, $-NHCONHR^B$, $-NR^ACONHR^B$, $-NHCONR^AR^B$, or $-NR^ACONR^AR^B$ wherein R^A and R^B are independently a $(C_1\text{-}C_6)$alkyl group.

As used herein the term "salt" includes base addition, acid addition and quaternary salts. Compounds of the invention which are acidic can form salts, including pharmaceutically or veterinarily acceptable salts, with bases such as alkali metal hydroxides, e.g. sodium and potassium hydroxides; alkaline earth metal hydroxides e.g. calcium, barium and magnesium hydroxides; with organic bases e.g. N-ethyl piperidine, dibenzylamine and the like. Those compounds (I) which are basic can form salts, including pharmaceutically or veterinarily acceptable salts with inorganic acids, e.g. with hydrohalic acids such as hydrochloric or hydrobromic acids, sulphuric acid, nitric acid or

phosphoric acid and the like, and with organic acids e.g. with acetic, tartaric, succinic, fumaric, maleic, malic, salicylic, citric, methanesulphonic and p-toluene sulphonic acids and the like.

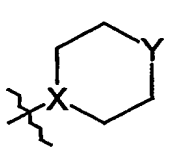
Some compounds of the invention contain one or more actual or potential chiral centres because of the presence of asymmetric carbon atoms. The presence of several asymmetric carbon atoms gives rise to a number of diastereoisomers with R or S stereochemistry at each chiral centre. The invention includes all such diastereoisomers and mixtures thereof.

In the compounds of the invention:

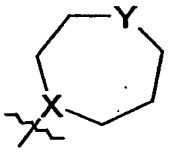
Ar may be, for example, a 2-hydroxyphenyl group which may be further substituted, for example by one or more of hydroxy, ethyl, chloro, bromo, or phenyl groups;

R_1 and R_2 may be, for example, hydrogen, methyl, ethyl, n- or iso-propyl, or hydroxyethyl. Hydrogen is presently preferred in the case of R_1, and hydrogen or methyl is presently preferred in the case of R_2;

Ring A may be, for example, a ring of formula (IIA) or (IIB):



(IIA)



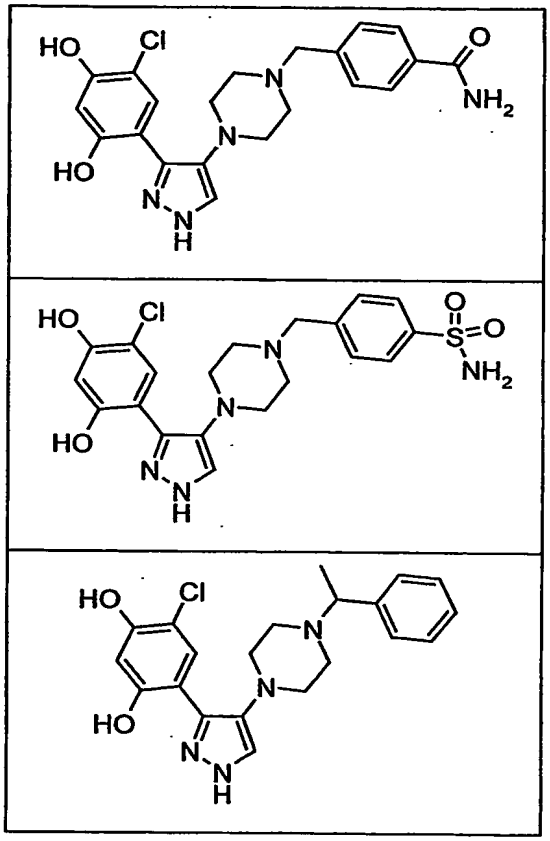
(IIB)

wherein X represents CH or N, and Y represents CH, O, S or NH, with optional substituents on ring carbons selected from any of those listed above in the definition of "substituted", and optional substituents on a Y nitrogen selected from those of formula $-(Alk^1)_p-(Z)_r-(Alk^2)_s-Q$ (as defined above). Presently it is preferred that ring A is a piperazine ring of formula (IIA) wherein X is N and Y is NR^A wherein R^A is hydrogen or optionally substituted C_1-C_6

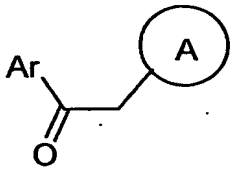
alkyl, or R^A is a radical of formula -(Alk^1)-Q, wherein Alk^1 is a C_1-C_3 alkylene radical and Q is optionally substituted phenyl, pyridyl, furyl, thienyl, oxadiazolyl, imidazolyl or morpholinyl.

Specific examples of substituted piperazine rings which may be present as ring A of the compounds of the invention are those of the compounds of the Examples herein.

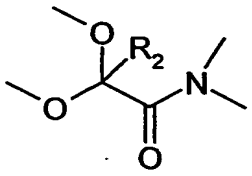
Specific compounds of the invention include those of the Examples herein and the following:



Compounds of the invention may be prepared by methods analogous to those used in the Examples herein, and in general are accessible by reaction of a compound of formula (IIA) with a compound of formula (IIB)

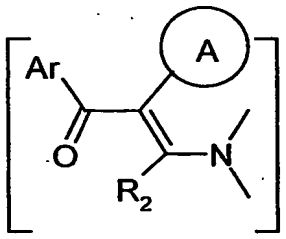


(IIA)



(IIB)

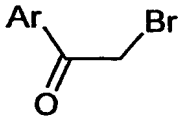
to form an intermediate compound of formula (IIC)



(IIC)

which is then reacted with the hydrazine H_2N-NHR_1 to form a mixture of the two pyrazole compounds (1A) and (IB), which may then be then separated. Of course it may be desirable to protect any potentially reactive groups in Ar, ring A and the substituents R1 and R2 during the above reactions and to remove the protecting groups subsequently.

Compounds of formula (IIA) may be prepared by nucleophilic displacement of bromine from a compound of formula (III) by an anion of ring A:



(III)

Some compounds of the invention are accessible by chemical modification of other compounds of the invention made by the above general method.

The compounds of the invention are inhibitors of HSP90 and are thus useful in the treatment of diseases which are mediated by excessive or inappropriate HSP90 activity such as cancers; viral diseases such as Hepatitis C (HCV)

(Waxman, 2002); Immunosupression such as in transplantation (Bijlmakers, 2000 and Yorgin, 2000); Anti-inflammatory diseases (Bucci, 2000) such as Rheumatoid arthritis, Asthma, MS, Type I Diabetes, Lupus, Psoriasis and Inflammatory Bowel Disease; Cystic fibrosis (Fuller, 2000); Angiogenesis-related diseases (Hur, 2002 and Kurebayashi, 2001): diabetic retinopathy, haemangiomas, psoriasis, endometriosis and tumour angiogenesis. Also an Hsp90 inhibitor of the invention may protect normal cells against chemotherapy-induced toxicity and be useful in diseases where failure to undergo apoptosis is an underlying factor. Such an Hsp90 inhibitor may also be useful in diseases where the induction of a cell stress or heat shock protein response could be beneficial, for example, protection from hypoxia-ischemic injury due to elevation of Hsp70 in the heart (Hutter, 1996 and Trost, 1998) and brain (Plumier, 1997 and Rajder, 2000). An Hsp90 inhibitor could also be useful in diseases where protein misfolding or aggregation is a major causal factor , for example, scrapie/CJD, Huntingdon's and Alzheimer's (Sittler, 2001; Trazelt, 1995 and Winklhofer, 2001).

Accordingly, the invention also provides:

(i) a method of treatment of diseases or conditions mediated by excessive or inappropriate HSP90 activity in mammals, in particular in humans, which method comprises administering to the mammal an effective amount of a compound of formula (IA) or (IB) above; and

(ii) a compound of formula (IA) or (IB) above, for use in human or veterinary medicine, particularly in the treatment of diseases or conditions mediated by by excessive or inappropriate HSP90 activity; and

(iii) the use of a compound of formula (IA) or (IB) above in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by excessive or inappropriate HSP90 activity.

It will be understood that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific

compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the causative mechanism and severity of the particular disease undergoing therapy. In general, a suitable dose for orally administrable formulations will usually be in the range of 0.1 to 3000 mg once, twice or three times per day, or the equivalent daily amount administered by infusion or other routes. However, optimum dose levels and frequency of dosing will be determined by clinical trials as is conventional in the art.

The compounds with which the invention is concerned may be prepared for administration by any route consistent with their pharmacokinetic properties. The orally administrable compositions may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical, or sterile parenteral solutions or suspensions. Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinyl-pyrrolidone; fillers for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants for example potato starch, or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For topical application to the skin, the drug may be made up into a cream, lotion or ointment. Cream or ointment formulations which may be used for the drug are conventional formulations well known in the art, for example as described in standard textbooks of pharmaceutics such as the British Pharmacopoeia.

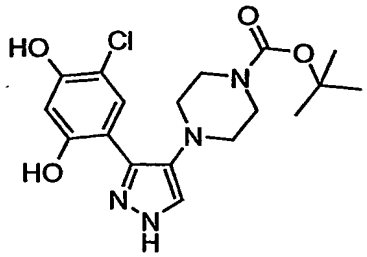
The active ingredient may also be administered parenterally in a sterile medium. Depending on the vehicle and concentration used, the drug can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

The following examples illustrate the preparation and activities of specific compounds of the invention.

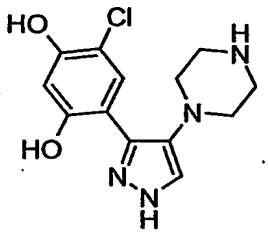
Example 1 gave result 'B' in the ATPase assay and Example 2 gave result 'A'

Example 1: **4-[3-(5-Chloro-2,4-dihydroxy-phenyl)-1H-pyrazol-4-yl]-piperazine-1-carboxylic acid tert-butyl ester,** and

Example 2: **4-Chloro-6-(4-piperazin-1-yl-1H-pyrazol-3-yl)-benzene-1,3-diol**

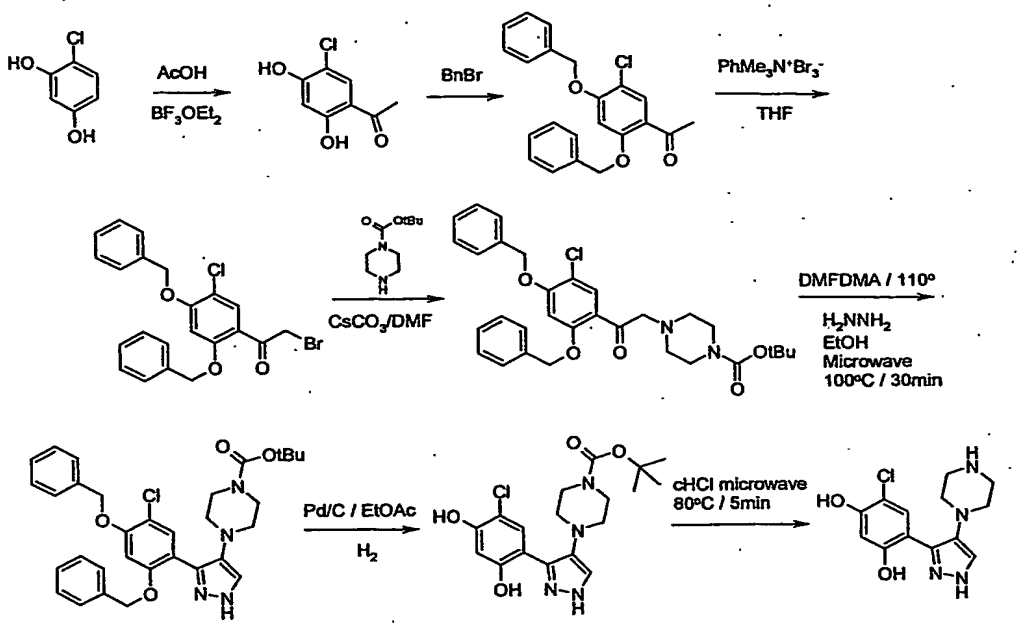


Example 1



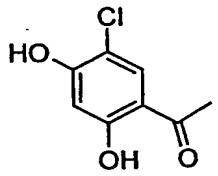
Example 2

Scheme 1: Synthesis of piperazinopyrazoles.



Step 1

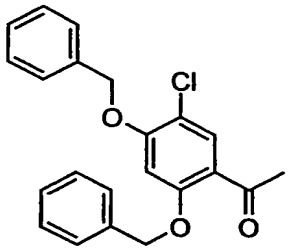
1-(5-Chloro-2,4-dihydroxy-phenyl)-ethanone



Acetic acid (17.5mL) was added dropwise to a suspension of 4-chlororesorcinol (42.5g, 0.293mmol) in boron trifluoride etherate (200mL) under a nitrogen atmosphere. The reaction mixture was heated at 90°C for 3.5 hours and then allowed to cool to room temperature. A solid had formed after around 1 hour of cooling. The mixture was poured into 700mL of a 10% w/v aqueous sodium acetate solution. This mixture was stirred vigorously for 2.5 hours. A light brown solid had formed which was filtered, washed with water and air-dried overnight to afford 1-(5-chloro-2,4-dihydroxy-phenyl)-ethanone (31.6g, 58%). LCMS: $[M-H]^+$ 185.

Step 2

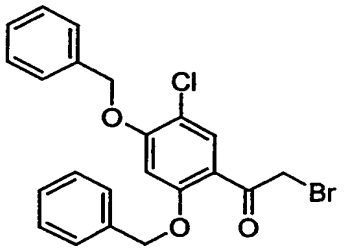
1-(2,4-Bis-benzyloxy-5-chloro-phenyl)-ethanone



Benzyl bromide (30mL) was added to a mixture of 1-(5-chloro-2,4-dihydroxy-phenyl)-ethanone (20g, 0.107moles) and potassium carbonate (37g, 2.5 equiv) in acetonitrile (350mL). The mixture was heated at reflux for 6 hours then allowed to cool and stirred overnight. The mixture was filtered and the solids were washed with dichloromethane (3 x 100mL). The combined organic extracts were evaporated in vacuo to leave a pale yellow solid which was triturated with a mixture of hexane (350mL) / ethyl acetate (15mL) and filtered to give an off-white solid, 1-(2,4-bis-benzyloxy-5-chloro-phenyl)-ethanone (35.4g, 90%). 1H NMR (400MHz) consistent with structure.

Step 3

1-(2,4-Bis-benzyloxy-5-chloro-phenyl)-2-bromo-ethanone

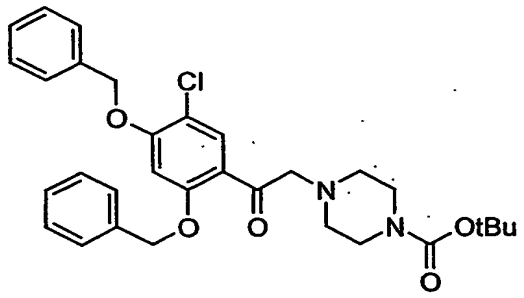


Phenyltrimethylammonium tribromide (7.5g, 0.02mol) was added portionwise to a stirred solution of 1-(2,4-Bis-benzyloxy-5-chloro-phenyl)-ethanone (7.09g, 0.019mol) in tetrahydrofuran (100ml) and the mixture was stirred for 2h. The mixture was partitioned between water (100ml) and diethyl ether (2x50ml). The combined organic phases were dried over magnesium sulphate and concentrated to give a beige solid. Crystallisation from toluene (100ml) gave 1-(2,4-Bis-benzyloxy-5-chloro-phenyl)-2-bromo-ethanone as a white solid (4.5g)

LC retention time 2.97 minutes, no ion (Run time 3.75min)

Step 4

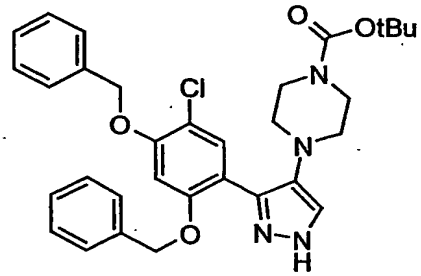
4-[2-(2,4-Bis-benzyloxy-5-chloro-phenyl)-2-oxo-ethyl]-piperazine-1-carboxylic acid tert-butyl ester



Cesium carbonate (2.95g, 9mmol) was added in three portions to a stirred solution of 1-(2,4-Bis-benzyloxy-5-chloro-phenyl)-2-bromo-ethanone (4.4g, 9mmol) and piperazine-1-carboxylic acid tert-butyl ester (1.74g, 9mmol) in dimethylformamide (20ml). The suspension was stirred for 2h then partitioned between water (200ml) and ethyl acetate (3x50ml). The combined organic extracts were washed with water (100ml), dried over magnesium sulphate and concentrated to give 4-[2-(2,4-Bis-benzyloxy-5-chloro-phenyl)-2-oxo-ethyl]-piperazine-1-carboxylic acid tert-butyl ester as a yellow oil (4g)
LC retention time 2.53 minutes $[M+H]^+$ 551.5 (Run time 3.75min)

Step 5

4-[3-(2,4-Bis-benzyloxy-5-chloro-phenyl)-1H-pyrazol-4-yl]-piperazine-1-carboxylic acid tert-butyl ester



A solution of 4-[2-(2,4-Bis-benzyloxy-5-chloro-phenyl)-2-oxo-ethyl]-piperazine-1-carboxylic acid tert-butyl ester (2g, 3.6mmol) in dimethylformamide dimethylacetal (4ml) was heated at reflux for 3h. A further quantity of dimethylformamide dimethylacetal (15ml) was added, and the mixture was heated at reflux for 4h. The mixture was split into 7 microwave

vessels. Ethanol (1ml) and hydrazine hydrate (1ml) was added to each microwave vessel, and each was heated at 120°C for 5 minutes. The contents of all the vessels were combined and partitioned between water (50ml) and dichloromethane (3x30ml). The combined organic phases were concentrated and purified on a bond elute cartridge (20g) eluting with hexane, followed by hexane:ether; 4:1 then 1:1 then 1:2 then 1:4 gave 4-[3-(2,4-Bis-benzyloxy-5-chloro-phenyl)-1H-pyrazol-4-yl]-piperazine-1-carboxylic acid tert-butyl ester as a white solid (620mg)

LC retention time 2.98 minutes $[M+H]^+$ 575.5 (Run time 3.75min)

Step 6

4-[3-(5-Chloro-2,4-dihydroxy-phenyl)-1H-pyrazol-4-yl]-piperazine-1-carboxylic acid tert-butyl ester (Example 1)

A solution of 4-[3-(2,4-Bis-benzyloxy-5-chloro-phenyl)-1H-pyrazol-4-yl]-piperazine-1-carboxylic acid tert-butyl ester (230mg, 0.4mmol) in ethyl acetate (15ml) was hydrogenated over 10% palladium on carbon for 1.5h. The suspension was filtered through celite, washing with dichloromethane:ethanol (1:1). The filtrate was concentrated to leave 4-[3-(5-chloro-2,4-dihydroxy-phenyl)-1H-pyrazol-4-yl]-piperazine-1-carboxylic acid tert-butyl ester (Example 1) as a white solid (72mg)

LC retention time 2.24 minutes $[M+H]^+$ 395.3 (Run time 3.75min)

Step 7

4-Chloro-6-(4-piperazin-1-yl-1H-pyrazol-3-yl)-benzene-1,3-diol (Example 2)

Method A

A mixture of 4-[3-(2,4-Bis-benzyloxy-5-chloro-phenyl)-1H-pyrazol-4-yl]-piperazine-1-carboxylic acid tert-butyl ester (25mg, 0.06mmol) and

concentrated hydrochloric acid (1ml) was heated in the microwave at 80°C for 5min. The mixture was evaporated to dryness, azeotroping with toluene to give 4-chloro-6-(4-piperazin-1-yl-1H-pyrazol-3-yl)-benzene-1,3-diol (10mg) (Example 2)

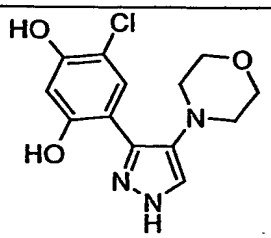
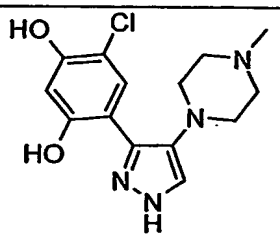
LC retention time 1.37 minutes $[M+H]^+$ 295.2 (Run time 3.75min)

Method B

Boron trichloride (1M solution in dichloromethane; 8ml, 8mmol) was added dropwise to a solution of 4-[3-(2,4-Bis-benzyloxy-5-chloro-phenyl)-1H-pyrazol-4-yl]-piperazine-1-carboxylic acid tert-butyl ester (1.5g, 2.6mmol) in dichloromethane (15ml) at 0°C. The resulting mixture was stirred at room temperature for 1h, then basified with saturated sodium bicarbonate solution. The suspension was concentrated *in vacuo*, azeotroping with toluene until the residue was dry. The residue was triturated with dichloromethane:ethanol (1:1; 15ml) and filtered. The filtrate was purified on a bond elute cartridge (20g) eluting with dichloromethane:ethanol:ammonia, 50:8:1 then 20:8:1 to give 4-chloro-6-(4-piperazin-1-yl-1H-pyrazol-3-yl)-benzene-1,3-diol as a pale yellow solid (400mg) (Example 2)

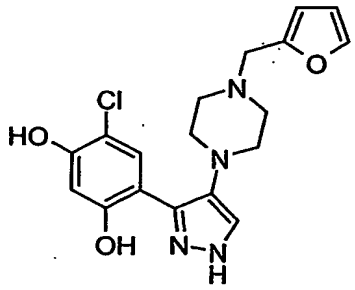
LC retention time 1.37 minutes $[M+H]^+$ 295.2 (Run time 3.75min)

The compounds in the following table were prepared as described in scheme 1 using the corresponding amine, and were purified using HPLC The entries in the column "Hsp90 IC50" are the results obtained in the ATPase assay described below.

Example	Structure	MH+	Hsp90 IC50
3		296	B
4		309	A

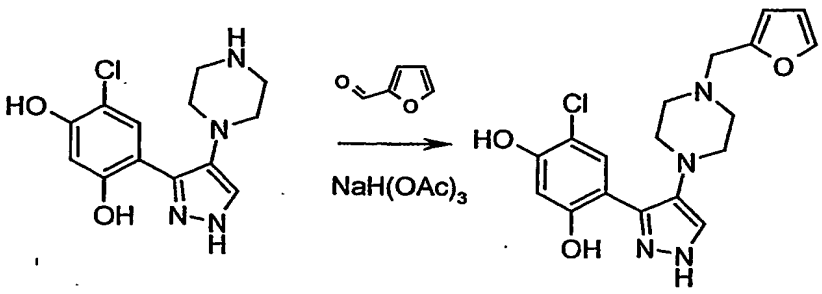
Example 5

4-Chloro-6-[4-(4-furan-2-ylmethyl-piperazin-1-yl)-1H-pyrazol-3-yl]-benzene-1,3-diol



this compound was made by the route summarised in Scheme 2:

Scheme 2: Reductive aminations of piperazines.

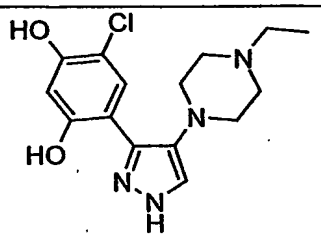


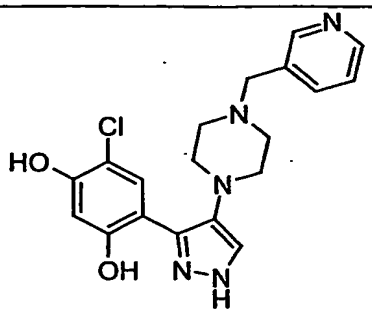
Sodium triacetoxyborohydride (150mg, 0.7mmol) was added in one portion to a mixture of 4-chloro-6-(4-piperazin-1-yl-1H-pyrazol-3-yl)-benzene-1,3-diol (43mg, 0.146mmol), furfuraldehyde (0.025ml, 0.3mmol), acetic acid (0.5ml) and dichloromethane (1ml). Stirring under nitrogen was continued for 3h, and the reaction mixture was partitioned between water (10ml) and dichloromethane (3x10ml). The combined organic phases were dried over magnesium sulphate and concentrated and purified on a bond elute cartridge (5g) eluting with dichloromethane:ethanol:ammonia (100:8:1) gave 4-chloro-6-[4-(4-furan-2-ylmethyl-piperazin-1-yl)-1H-pyrazol-3-yl]-benzene-1,3-diol as a white solid (10mg).

LC retention time 1.68 minutes $[M+H]^+$ 375.3 (Run time 3.75min)

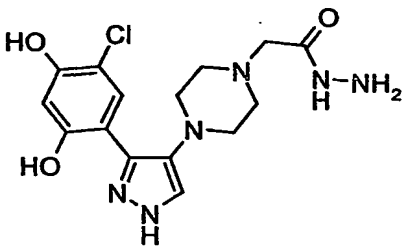
Example 5 had activity 'B' in the ATPase assay.

Examples 6 and 7 were also prepared according to Scheme 2 using acetaldehyde and 3-pyridyl aldehyde, respectively. The entries in the column "Hsp90 IC50" are the results obtained in the ATPase assay described below.

Example	Structure	MH+	Hsp90 IC50
6		323	A

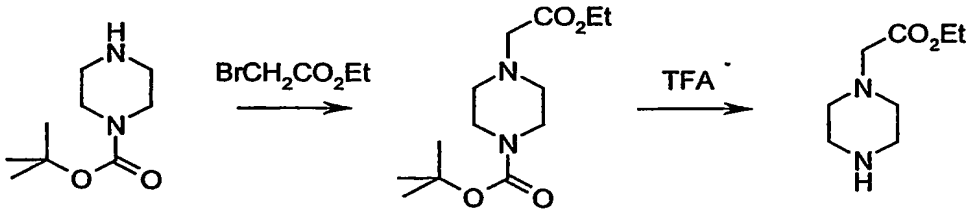
Example	Structure	MH+	Hsp90 IC50
7		386	A

Example 8



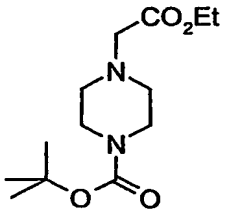
Example 8 was prepared as described in the following 2 schemes:

Scheme 3: Synthesis of piperazine acetic acid ethyl ester.



Step 1

4-Ethoxycarbonylmethyl-piperazine-1-carboxylic acid tert-butyl ester



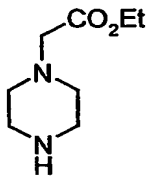
Piperazine-1-carboxylic acid tert-butyl ester (2.62g, 14mmol), cesium carbonate (5g, 15mmol) and ethyl bromoacetate (1.56ml, 14mmol) was stirred

at room temperature for 1h. The mixture was partitioned between water (200ml) and diethyl ether (2x100ml). The combined organic phases were dried over magnesium sulphate and concentrated to give a yellow oil which crystallised to give 4-ethoxycarbonylmethyl-piperazine-1-carboxylic acid tert-butyl ester as a pale yellow solid (2.6g)

^{1}H N.M.R ($CDCl_3$) δ = 1.24 (3H, t, J = 7.1Hz), 1.43 (9H, s), 2.49 (4H, t, J = 5Hz), 3.20 (2H, s), 3.44 (4H, t, J = 4.8Hz), 4.16 (2H, q, J = 7.1Hz).

Step 2

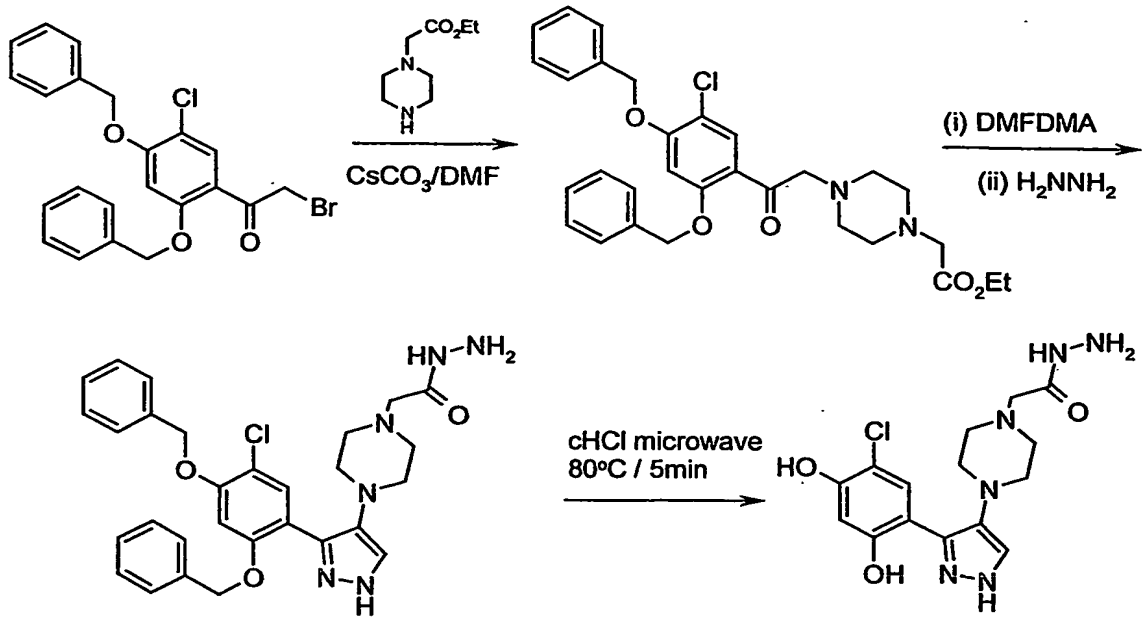
Piperazin-1-yl-acetic acid ethyl ester



A solution of 4-ethoxycarbonylmethyl-piperazine-1-carboxylic acid tert-butyl ester in 90% trifluroacetic acid (5ml) was stirred for 3h. The mixture was basified with saturated sodium bicarbonate solution and concentrated. The residue was triturated with ethylacetate (30ml) and filtered. The filtrate was concentrated to leave piperazin-1-yl-acetic acid ethyl ester as a yellow oil (ca 1.5g)

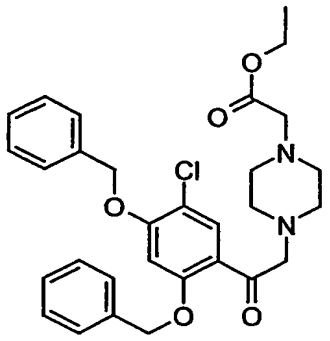
^{1}H N.M.R ($CDCl_3$) δ = 1.18 (3H, t, J = 7.1Hz), 2.40 (4H, t, J = 4.1Hz), 2.70 (4H, t, J = 4.5Hz), 3.13 (2H, s), 3.45 (1H, br s), 4.01 (2H, q, J = 7.1Hz)

Scheme 4: Synthesis of acyl hydrazide



Step 3

{4-[2-(2,4-Bis-benzyloxy-5-chloro-phenyl)-2-oxo-ethyl]-piperazin-1-yl}-acetic acid ethyl ester



Prepared as described in Scheme 1 using piperazin-1-yl-acetic acid ethyl ester

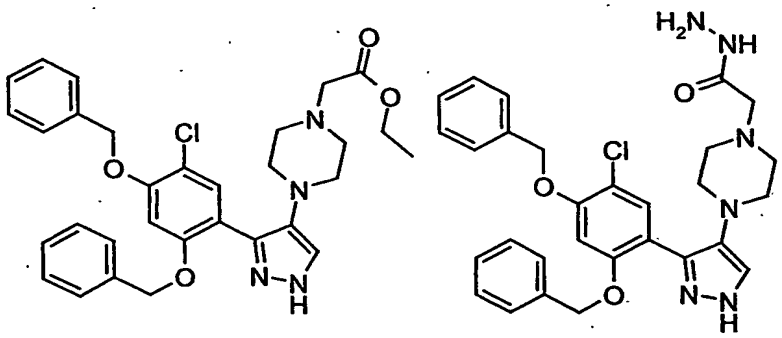
LC retention time 2.32 minutes $[M+H]^+$ 537.5 (Run time 3.75min)

Step 4

{4-[3-(2,4-Bis-benzyloxy-5-chloro-phenyl)-1H-pyrazol-4-yl]-piperazin-1-yl}-acetic acid ethyl ester

and

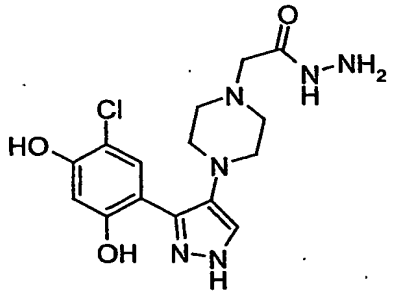
{4-[3-(2,4-Bis-benzyloxy-5-chloro-phenyl)-1H-pyrazol-4-yl]-piperazin-1-yl}-acetic acid hydrazide



A solution of {4-[2-(2,4-Bis-benzyloxy-5-chloro-phenyl)-2-oxo-ethyl]-piperazin-1-yl}-acetic acid ethyl ester (1.5g, 2.80mmol) in dimethylforamide dimethylacetal (4ml) was heated at 140°C in the microwave for 30min. The solution was split into two portions and each was mixed with hydrazine hydrate (0.1ml) and ethanol (2ml) and heated in the microwave at 100oC for 5min. The combined mixture was concentrated and purified on a bond elute cartridge to give {4-[3-(2,4-Bis-benzyloxy-5-chloro-phenyl)-1H-pyrazol-4-yl]-piperazin-1-yl}-acetic acid ethyl ester (230mg) and {4-[3-(2,4-Bis-benzyloxy-5-chloro-phenyl)-1H-pyrazol-4-yl]-piperazin-1-yl}-acetic acid hydrazide (150mg).

Step 5

{4-[3-(5-Chloro-2,4-dihydroxy-phenyl)-1H-pyrazol-4-yl]-piperazin-1-yl}-acetic acid hydrazide (Example 8)



Prepared from {4-[3-(2,4-Bis-benzyloxy-5-chloro-phenyl)-1H-pyrazol-4-yl]-piperazin-1-yl}-acetic acid hydrazide, analogously to Example 2, Step 7, Method A

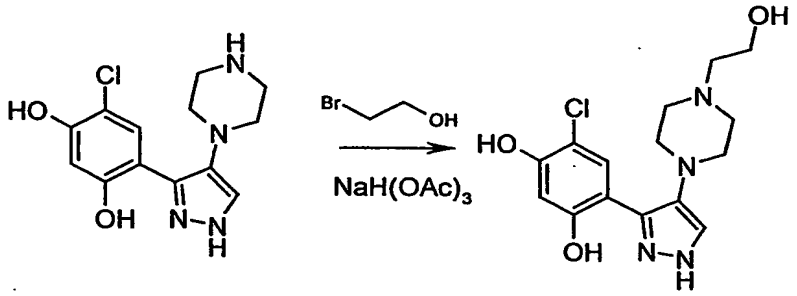
LC retention time 1.40 minutes $[M+H]^+$ 367.3 (Run time 3.75min)

Example 8 had activity 'B' in the ATPase assay.

Example 9

4-Chloro-6-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-1H-pyrazol-3-yl}-benzene-1,3-diol

Scheme 5: Alkylation of piperazines:

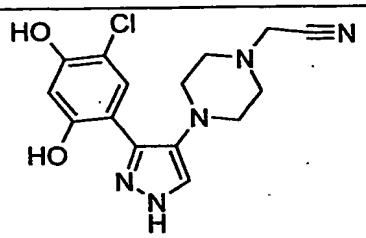
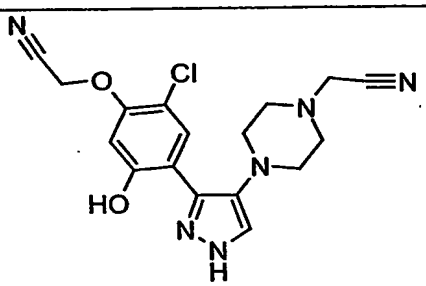
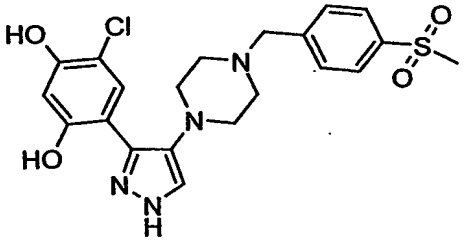
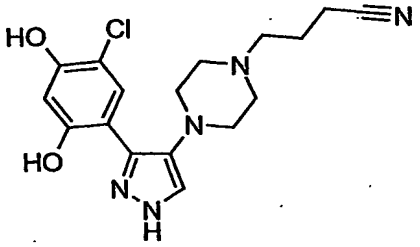


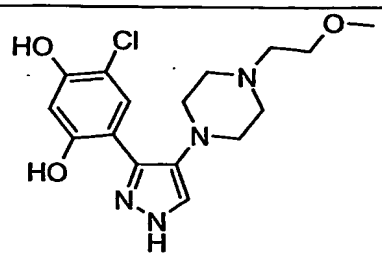
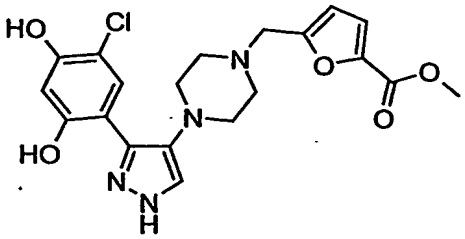
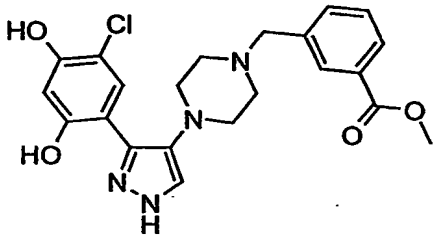
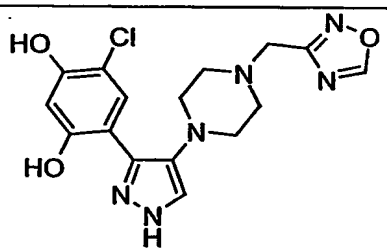
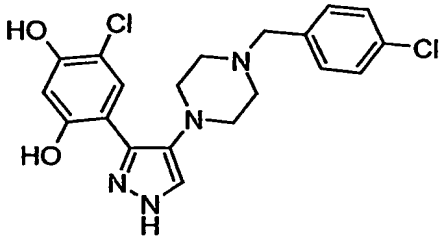
A mixture of 4-chloro-6-(4-piperazin-1-yl-1H-pyrazol-3-yl)-benzene-1,3-diol (43mg, 0.146mmol), cesium carbonate (48mg, 0.146mmol), 2-bromoethanol (0.025ml, 0.35mmol) and dimethylformamide (1ml) was stirred at room temperature for 3 days. The mixture was evaporated to dryness and applied to a bond elute cartridge (5g) with dichloromethane:methanol (49:1), then eluting with dichloromethane followed by dichloromethane:ethanol:ammonia (50:8:1 then 20:8:1) gave 4-chloro-6-{4-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-1H-pyrazol-3-yl}-benzene-1,3-diol as a white solid (10mg)

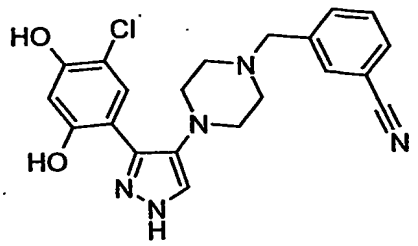
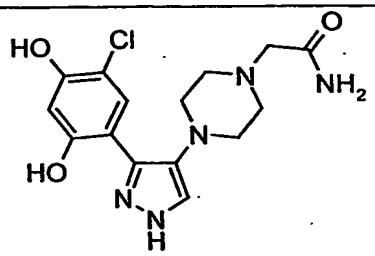
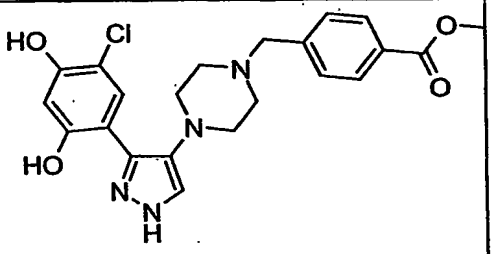
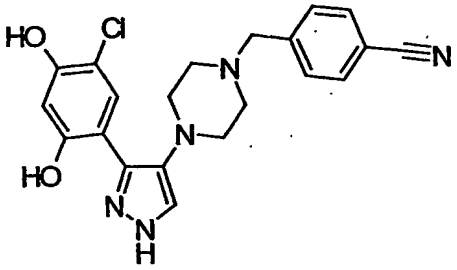
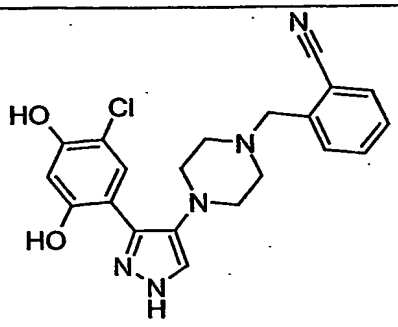
LC retention time 1.36 minutes $[M+H]^+$ 339.3 (Run time 3.75min)

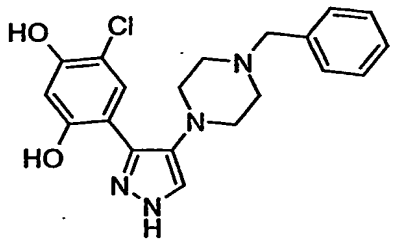
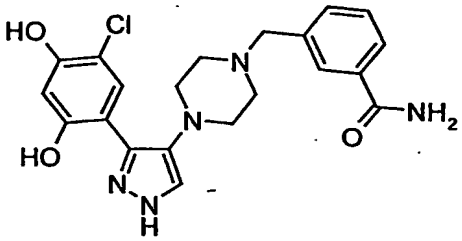
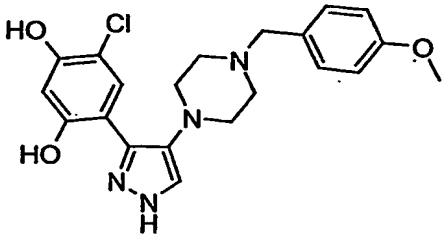
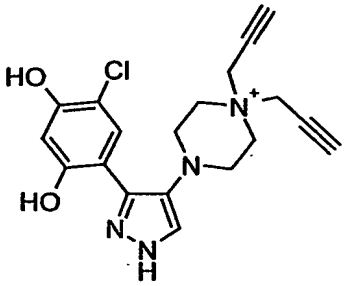
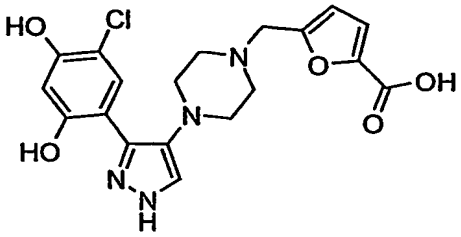
Example 9 had activity 'B' in the ATPase assay.

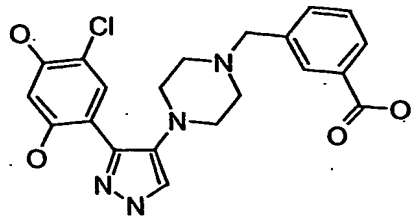
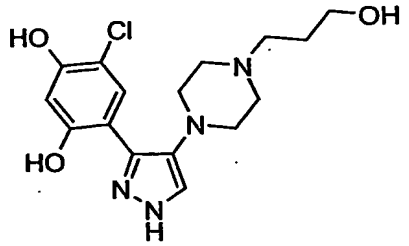
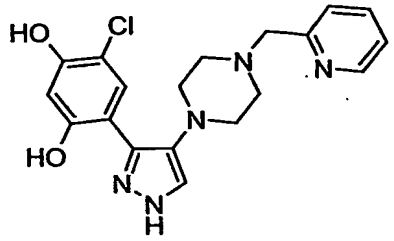
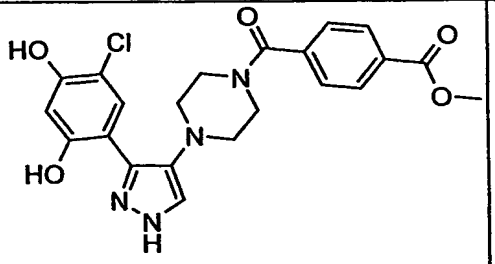
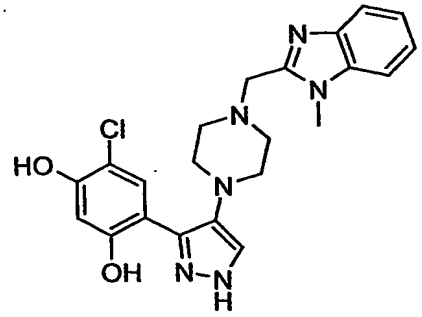
Examples 10 to 34 were prepared by the method summarised in Scheme 5, using the appropriate alkylating agent. The entries in the column "Hsp90 IC50" are the results obtained in the ATPase assay described below:

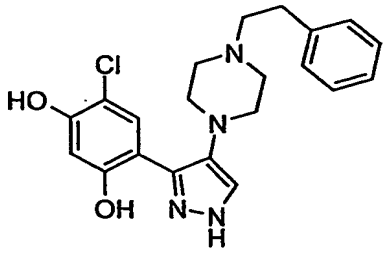
Example	Structure	MH+	Hsp90 IC50
10		334	B
11		373	B
12		463	A
13		361	A

Example	Structure	MH+	Hsp90 IC50
14		353	A
15		434	A
16		444	A
17		378	A
18		420	A

Example	Structure	MH+	Hsp90 IC50
19		411	A
20		353	A
21		444	A
22		411	A
23		411	A

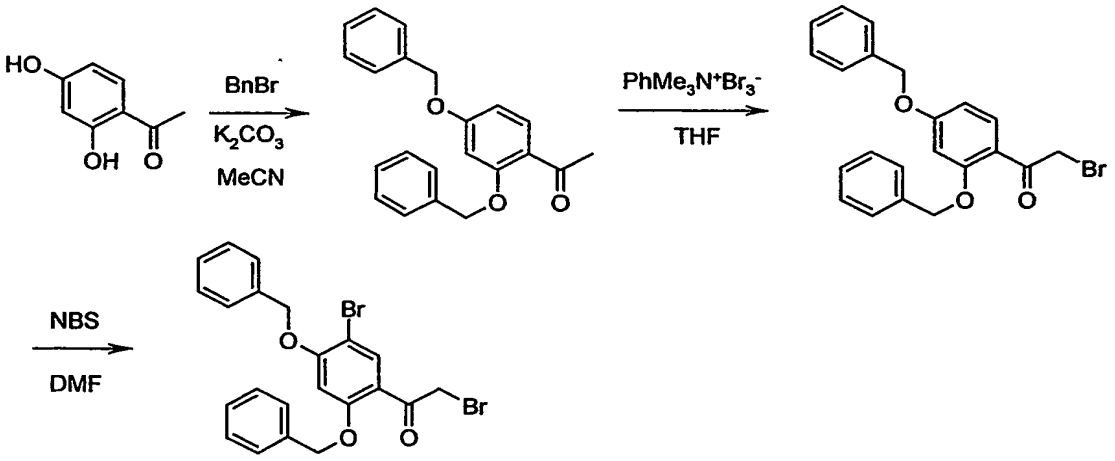
Example	Structure	MH+	Hsp90 IC50
24		386	A
25		429	A
26		416	A
27		373	A
28		420	A

Example	Structure	MH+	Hsp90 IC50
29		430	A
30		354	A
31		387	A
32		458	B
33		439	B

Example	Structure	MH+	Hsp90 IC50
34		399	A

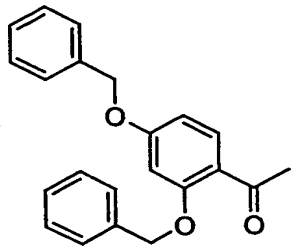
Compounds where the resorcinol ring was substituted with bromine were prepared using the Scheme 1 synthesis modified as described in Scheme 6. The first 3 steps of the synthesis gave the required bromo intermediate which was taken through the subsequent steps as in Scheme 1:

Scheme 6: Synthesis of bromo intermediate:



Step 1

1-(2,4-Bis-benzyloxyphenyl)-ethanone

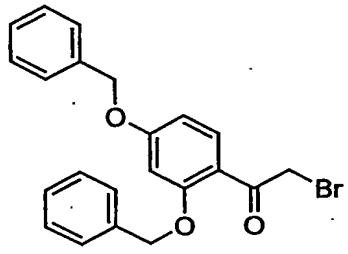


Benzyl bromide (35.6 mL, 0.3 mol) was added to a suspension of 2,4-dihydroxyacetophenone (15g, 0.1 mol) and potassium carbonate (41.4 g, 0.3 mol) in acetonitrile (150 mL) and the mixture stirred overnight. After concentration to dryness, the residues were resuspended in dichloromethane (100 mL) and washed with water (100 mL). The organic phase was dried over magnesium sulphate and concentrated. Trituration with hexanes, filtration and drying in vacuo gave 1-(2,4-Bis-benzyloxyphenyl)-ethanone as a white powder (26g).

LC retention time 2.83 minutes, $[M+H]^+$ 333.3 (Run time 3.75min)

Step 2

1-(2,4-Bis-benzyloxyphenyl)-2-bromo-ethanone



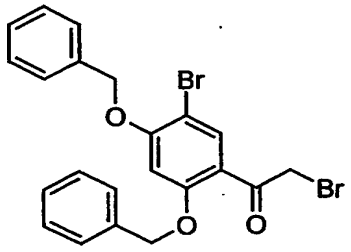
Phenyltrimethylammonium tribromide (5.6g, 0.015mol) was added portionwise to a stirred solution of 1-(2,4-Bis-benzyloxyphenyl)-ethanone (5.0g, 0.015mol) in tetrahydrofuran (50ml) and the mixture was stirred for 2h. The mixture was partitioned between water (50ml) and diethyl ether (2x50ml). The combined organic phases were dried over magnesium sulphate and concentrated to

give 1-(2,4-Bis-benzyloxyphenyl)-2-bromo-ethanone as a beige solid which was used without further purification.

LC retention time 2.89 minutes, $[M+H]^+$ 411.2 and 413.2 (Run time 3.75min)

Step 3

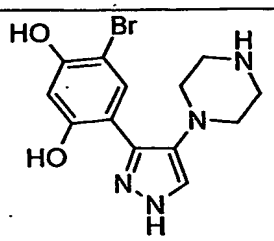
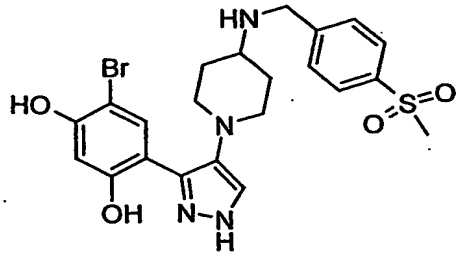
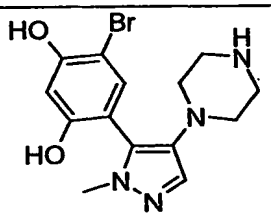
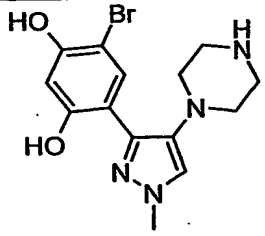
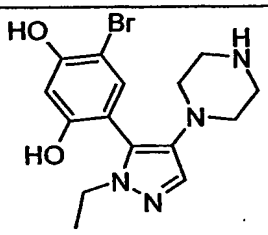
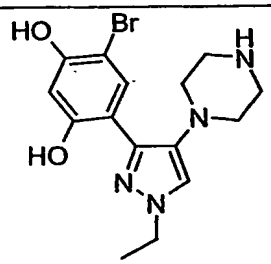
1-(2,4-Bis-benzyloxy-5-bromo-phenyl)-2-bromo-ethanone

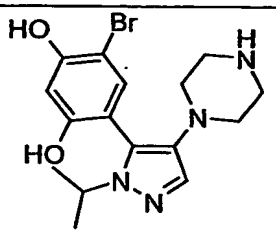
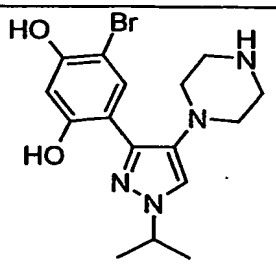
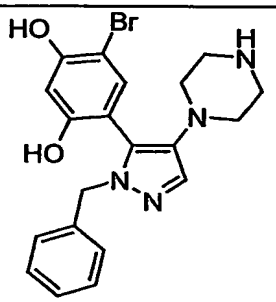
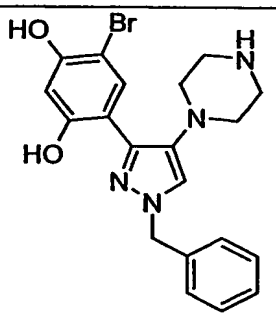
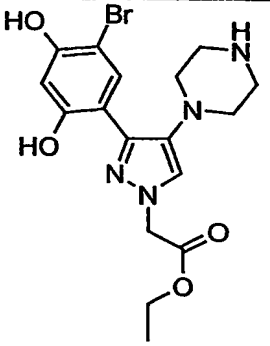


N-bromo succinimide (2.67 g, 0.015mol) was added to a stirred solution of crude 1-(2,4-Bis-benzyloxyphenyl)-2-bromo-ethanone (*ca.* 6.16g, 0.015mol) in dimethylformamide (50ml) and the mixture was stirred for 18h. The mixture was concentrated to dryness, dissolved in dichloromethane (50 mL) and washed with (2x50ml). The combined organic phases were dried over magnesium sulphate and concentrated to give 1-(2,4-Bis-benzyloxy-5-bromo-phenyl)-2-bromo-ethanone as a white solid, which was used without further purification.

LC retention time 2.99 minutes, $[M+Na]^+$ 511.2, 513.2 and 515.2 (Run time 3.75min)

The bromo-substituted compounds in the following Table were prepared from the above 1-(2,4-bis-benzyloxy-5-bromo-phenyl)-2-bromo-ethanone intermediate by methods analogous to those used for the preparation of the chloro-substituted compounds of the previous Examples Bromo examples 35-45 were prepared using Scheme 6. Again the entries in the column "Hsp90 IC50" are the results obtained in the ATPase assay described below:

Example	Structure	MH+	Hsp90 IC50
35		339,341	B
36		521,523	A
37		353,355	B
38		353,355	B
39		367,369	B
40		367,369	B

Example	Structure	MH+	Hsp90 IC50
41		381,383	B
42		381,383	B
43		429,431	B
44		429,431	B
45		425,427	B

Biological Results

The intrinsic ATPase activity of HSP90 may be measured using yeast HSP90 as a model system. The assay, based on the use of malachite green for the measurement of inorganic phosphate, was used to test the HSP90 inhibitory activity of the compounds of the Examples herein.

Malachite Green ATPase Assay

Materials

Chemicals are of the highest purity commercially available and all aqueous solutions are made up in AR water. Because of the need to minimise contamination with inorganic phosphate, precautions should be taken with solutions and apparatus used in the assays. Glassware and pH meters are rinsed with double distilled or deionised water before use and, wherever possible, plastic ware should be used. Gloves are worn for all procedures.

(1) Greiner 384-well (Greiner 781101) or Costar 384-well flat-bottomed polystyrene multiwell plates (VWR).

(2) Assay buffer of (a) 100mM Tris-HCl, pH 7.4, (b) 150mM KCl, (c) 6mM $MgCl_2$. Stored at room temperature.

(3) 0.0812% (w/v) malachite green (M 9636, Sigma Aldrich Ltd., Poole, UK). Stored at room temperature.

(4) 2.32% (w/v) polyvinyl alcohol USP (P 1097, Sigma Aldrich Ltd, Poole, UK) in boiling water (see Comment 1), allowed to cool, and stored at room temperature.

(5) 5.72% (w/v) ammonium molybdate in 6 M hydrochloric acid. Stored at room temperature.

(6) 34% (w/v) sodium citrate. Stored at room temperature.

(7) 100mM ATP, disodium salt, special quality (47699, Sigma Aldrich). Stored at -20°C.

(8) E. coli expressed yeast HSP90 protein, purified >95% (see, e.g., Panaretou et al., 1998) and stored in 50uL aliquots at -80°C .

Method

1. Dilute test compounds to 500μM in AR water (DMSO concentration will be 2.5%). Transfer 2.5μl of these compounds directly from the daughter plate to the assay plate, giving a final assay concentration of 100μM. To obtain 12 point IC50 values, perform serial dilutions 1:2 to produce a range of assay concentrations from 100μM to 97.6nM (2.5% DMSO), and transfer 2.5μl of each concentration into the assay plate. Column 1in the assay plate contains no compound, as a negative control. An additional row with no compound is also used as a background.
2. Prepare ATP by diluting 100mM stock to 925μM with assay buffer, and aliquot 5μl of diluted ATP to each well including controls (final assay concentration 370μM).
3. Add 5μl of buffer to background row.
4. Dilute enzyme preparation to 1.05μM with assay buffer, and aliquot 5μl into each compound well and to the negative control column.
5. Collect the reagents to the bottom of the well, cover plate with plate seal and incubate overnight at 37degC.
6. First thing in the morning prepare the Malachite Green Reagent. Add 2parts of Malachite Green Solution, 1 part of Polyvinyl Alcohol Solution, 1 part of Ammonium Molybdate Solution, and 2 parts of AR water.
7. Invert to mix, and leave for approximately 1 hour until the colour turns from brown to golden yellow.
8. Add 40μl of Malachite Green Reagent to each well, allow 5 mins for colour to develop.
9. Add 5μl of Sodium Citrate Reagent to each well (see comment 2)
10. Re-cover with plate seal and shake on plate shaker for at least 15 mins.
11. Measure Absorbance at 620nM using a suitable plate reader (e.g. Victor, Perkin Elmer Life Sciences, Milton Keynes, UK). Under these conditions, the control absorbance is 0.9 to 1.4, and the background is

0.2-0.35 giving a signal to noise ratio of ~12. The Z' factor calculated from data obtained using these conditions is between 0.6 and 0.9.

Comments

(1) The polyvinyl alcohol dissolves in boiling water with difficulty and stirring for 2-3 h is required.

(2) The time interval between addition of the malachite green reagent and the sodium citrate should be kept as short as possible in order to reduce the non-enzymatic hydrolysis of ATP. Once the sodium citrate is added, the colour is stable for up to 4 h at room temperature.

(3) Compounds can be added to the assay plates using a Biomek FX Robot (Beckman Coulter). A Multidrop 384 dispenser (Thermo Labsystems, Basingstoke, UK) can be conveniently used to add reagents to the plate.

(4) The assay conditions were optimised with respect to time, protein and substrate concentration in order to achieve minimal protein concentration whilst retaining signal to noise differential.

(5) Signal to noise (S/N) is calculated using the following equation:

$$(S-B)/\sqrt{(SD \text{ of } S)^2 + (SD \text{ of } B)^2}$$

(6) To determine specific activity of HSP90, a range of inorganic phosphate concentrations (0-10 μM) are prepared and the absorbance at 620 nm measured as described. Specific activity is calculated from the resulting calibration curve.

The compounds tested in the above assay were assigned to one of two activity ranges, namely A = <50μM; B = >50μM, and those assignments are reported above.

A growth inhibition assay was also employed for the evaluation of candidate HSP90 inhibitors:

Assessment of cytotoxicity by Sulforhodamine B (SRB) assay: calculation of 50% inhibitory concentration (IC_{50}).

Day 1

1) Determine cell number by haemocytometer.
2) Using an 8 channel multipipettor, add 160µl of the cell suspension (3600 cells/well or 2 x 10^4 cells/ml) to each well of a 96-well microtitre plate.
3) Incubate overnight at 37°C in a CO_2 incubator.

Day 2

4) Stock solutions of drugs are prepared, and serial dilutions of each drug are performed in medium to give final concentrations in wells.
5) Using a multipipettor, 40µl of drug (at 5x final concentration) is added to quadruplicate wells.
6) Control wells are at either side of the 96 well plates, where 40µl of medium is added.
7) Incubate plates in CO_2 incubator for 4 days (48 hours).

Day 6

8) Tip off medium into sink and immerse plate slowly into 10% ice cold trichloroacetic acid (TCA). Leave for about 30mins on ice.
9) Wash plates three times in tap water by immersing the plates into baths of tap water and tipping it off.
10) Dry in incubator.
11) Add 100µl of 0.4% SRB in 1%acetic acid to each well (except the last row (right hand)of the 96 well plate, this is the 0% control, ie no drug, no stain. The first row will be the 100% control with no drug, but with stain). Leave for 15 mins.
12) Wash off unbound SRB stain with four washes of 1% acetic acid.
13) Dry plates in incubator.

14) Solubilise SRB using 100µl of 10mM Tris base and put plates on plate shaker for 5 mins.

15) Determine absorbance at 540nm using a plate reader. Calculate mean absorbance for quadruplicate wells and express as a percentage of value for control, untreated wells.

16) Plot % absorbance values versus log drug concentration and determine the IC_{50}.

By way of illustration, the compound of Example 2 gave an IC50 in the 'A' range (<50uM) for the SRB growth arrest assay.

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A number of publications are cited above in order to more fully describe and disclose the invention and the state of the art to which the invention pertains. Full citations for these references are provided below. Each of these references is incorporated herein by reference in its entirety into the present disclosure.

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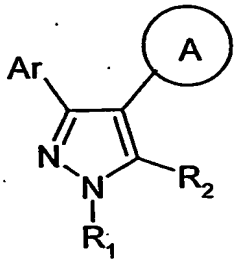
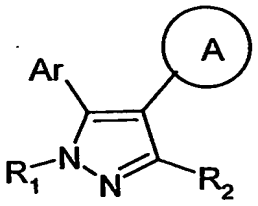
Claims:

1. A compound of formula (IA) or (IB) or a salt, N-oxide, hydrate or solvate thereof:



(IA)



(IB)

wherein

Ar is an optionally substituted aryl or heteroaryl radical;

R_1 is hydrogen or optionally substituted C_1-C_6 alkyl;

R_2 is hydrogen, optionally substituted cycloalkyl, cycloalkenyl, C_1-C_6 alkyl, C_1-C_6 alkenyl, or C_1-C_6 alkynyl; or a carboxyl, carboxamide or carboxyl ester group; and;

ring A is a non aromatic carbocyclic or heterocyclic ring wherein (i) a ring carbon is optionally substituted, and/or (ii) a ring nitrogen is optionally substituted by a group of formula $-(Alk^1)_p-(Z)_r-(Alk^2)_s-Q$ where

Alk^1 and Alk^2 are optionally substituted C_1-C_3 alkyl,

p, r and s are independently 0 or 1,

Z is –O-, -S-, -(C=O)-, $-SO_2-$, -C(=O)O-, $-C(=O)NR^A-$, $-SO_2NR^A-$, $-NR^AC(=O)-$, $-NR^ASO_2-$ or $-NR^A-$ wherein R^A is hydrogen or C_1-C_6 alkyl, and

Q is hydrogen or an optionally substituted carbocyclic or heterocyclic radical.

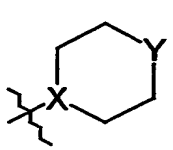
2. A compound as claimed in claim 1 wherein Ar is a 2-hydroxyphenyl group which is optionally further substituted.

3. A compound as claimed in claim 1 wherein Ar is a 2-hydroxyphenyl group further substituted by one or more of hydroxy, ethyl, chloro, bromo, or phenyl groups.

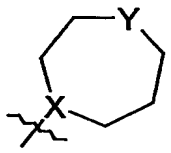
4. A compound as claimed in any of the preceding claims wherein R_1 and R_2 are independently hydrogen, methyl, ethyl, n- or iso-propyl, or hydroxyethyl.

5. A compound as claimed in any of claims 1 to 3 wherein R_1, is hydrogen and R_2 is hydrogen or methyl.

6. A compound as claimed in any of the preceding claims wherein ring A is a ring of formula (IIA) or (IIB):



(IIA)



(IIB)

wherein X represents CH or N, and Y represents CH, O, S or NH, wherein (i) a ring carbon is optionally substituted, and/or (ii) a ring nitrogen is optionally substituted by a group of formula $-(Alk^1)_p-(Z)_r-(Alk^2)_s-Q$ where

Alk^1 and Alk^2 are optionally substituted C_1-C_3 alkylene radicals,

p, r and s are independently 0 or 1,

Z is –O-, -S-, -(C=O)-, $-SO_2-$, -C(=O)O-, $-C(=O)NR^A-$, $-SO_2NR^A-$, $-NR^AC(=O)-$, $-NR^ASO_2-$ or $-NR^A-$ wherein R^A is hydrogen or C_1-C_6 alkyl, and

Q is hydrogen or an optionally substituted carbocyclic or heterocyclic radical.

7. A compound as claimed in claim 6 wherein Y is NR^A wherein R^A is a radical of formula $-(Alk^1)-Q$, wherein Alk^1 is a C_1-C_3 alkylene radical and Q is

optionally substituted phenyl, pyridyl, furyl, thienyl, oxadiazolyl, imidazolyl or morpholinyl.

8 A compound as claimed in claim 1 which is specifically named or disclosed herein or which is the subject of an Example herein.

9. A method of treatment of diseases or conditions mediated by excessive or inappropriate HSP90 activity in mammals, in particular in humans, which method comprises administering to the mammal an effective amount of a compound as claimed in any of the preceding claims.

10. A compound as claimed in any of claims 1 to 8, for use in human or veterinary medicine.

11. A compound as claimed in any of claims 1 to 8, for use in the treatment of diseases or conditions mediated by by excessive or inappropriate HSP90 activity.

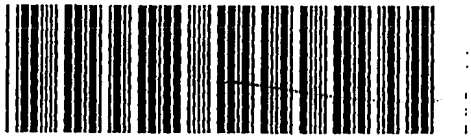
12. The use of a compound as claimed in any of claims 1 to 8 in the preparation of an agent for the management of diseases or conditions mediated by excessive or inappropriate HSP90 activity.

13. A method as claimed in claim 9, a compound for use as claimed in claim 10 or claim 11, or the use as claimed in claim 12 wherein the disease or condition is cancer.

14. A method as claimed in claim 9, a compound for use as claimed in claim 10 or claim 11, or the use as claimed in claim 12 wherein the disease or condition is a viral disease, transplant rejection, inflammatory disease, asthma, multiple sclerosis, Type I diabetes, lupus, psoriasis, inflammatory bowel disease, cystic fibrosis,angiogenesis-related disease, diabetic retinopathy, haemangioma, or endometriosis.

PCT Application

GB0305501



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